recited amino acid residues, but rather recites a single amino acid residue at position 275 (i.e., "R275"). Therefore it is submitted that the objection is moot, and should be withdrawn.

III. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-17, 21, 25-26, 28 and 30-32 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

The second paragraph of 35 U.S.C. §112 essentially requires precision and definiteness in claim language. A decision on whether a claim is indefinite requires a determination whether those skilled in the art would understand what is claimed when the claim is read in light of the specification. Seattle Box Co. v. Industrial Crating & Packing Inc., 221 USPQ 568, 574 (Fed. Cir. 1984). It is entirely proper to use the specification to interpret what the patentee meant by a word or phrase in the claim. E.I. Du Pont & Co. v. Phillips Petroleum Co., 7 USPQ2d 1129 (Fed. Cir. 1988). The test is whether one of ordinary skill in the art can determine with a reasonable degree of certainty what would be infringing and what would not. In re Marosi, 218 USPQ 289 (CAFC 1983); and In re Miller, 169 USPQ 597 (CCPA 1971).

A. Claim 1

In support of the rejection, The Action first states that Claim 1 is indefinite because the meaning of "R275" is

unclear as there is no reference sequence recited in the claim, and further because it is unclear as to what "aspartate 477 and lysine 429" refers. These positions are respectfully traversed.

The specification teaches the sequence of tissue type plasminogen activator protein (tPA) at page 1, lines 26-27, and at page 8, lines 5-12, and as shown in Figure 1. Therefore, residues 275, 477 and 429 are known. Furthermore, the single letter code for arginine of "R" is well known in the art, and it is defined in the specification that "R275" refers to the arginine residue at position 275 of tPA (see, e.g., page 3, lines 24-25, and page 8, line 8). Also, the three letter code is well known, such that the reference to "aspartate 477 and lysine 429" in claim 1 unambiguously refers to "ASP" and "LYS" shown in Figure 1C at positions 477 and 429, respectively.

One skilled in the art understands with clarity that "R275" refers to arginine at position 275 of the amino acid residue sequence of tPA shown in Figure 1, and understands with clarity that "aspartate 477 and lysine 429" refers to aspartic acid at position 477 and lysine at position 429 of the tPA sequence.

B. Claim 28

In support of the rejection, The Action also states that Claim 28 is indefinite as to the composition of the kit. This argument is respectfully traversed.

The content, formulation and use of diagnostic kits are generally well understood in the art, and therefore extensive details are not required, other than to identify the novel

components of the kit. Claim 28 specifies a kit "comprising the protein of claim 1", thereby identifying the unique aspect of the claimed kit. The specification further teaches diagnostic applications of the invention at page 11, lines 7-8, and at lines 19-25. It is submitted that the claim is definite, and clearly identifies to one skilled in the art the claimed invention. Therefore it is requested that the rejection of claim 28 for indefiniteness be withdrawn.

C. Claim 30 and 31

Claims 30 and 31 have been canceled without prejudice, rendering the rejection moot.

D. Claims 2-17, 21, 25, 26, 28 and 30-32

It is submitted that claims 2-17, 21, 25, 26, 28 and 30-32 are not indefinite for being dependent upon indefinite claim 1 for the reason that claim 1 is not indefinite according to the arguments above. Therefore it is requested that the rejection be withdrawn.

For the reasons above, it is requested that all rejections for alleged indefiniteness be withdrawn.

IV. Rejection Under 35 U.S.C. § 102(a)

Claims 1, 2, 5-8, 10-11, 15-16 and 30-31 were were rejected under 35 U.S.C. § 102(a) as being anticipated by Strandberg et al. (hereinafter "Strandberg"). These rejections are respectfully traversed.

The Court of Appeals for the Federal Circuit has repeatedly recognized that anticipation requires that each

and every element of the claimed invention be disclosed in the prior art reference and that the prior art reference be enabling, thus placing allegedly disclosed matter in the possession of the public. Akzo N.V. v. U.S. International Trade Commission, 808 F.2d 1471, 1 USPQ 2d 1241 (Federal Circuit 1986), certiorari denied, 107 S. Ct. 2470, 96 L. Ed. 2d 382. The proper inquiry under 35 U.S.C. § 102 is whether a prior publication bears within its four corners adequate directions for practice of the patent invention. Illinois Tool Works, Inc. v. Foster Grant Co., Inc., 395 F.Supp. 234 (D.C. Ill. 1974), affirmed 547 F.2d 1300, 192 USPQ 365, certiorari denied, 97 S.Ct. 2631, 53 L.Ed. 2d 243.

The issue is decided by identifying the elements of the claims, determining their meaning in light of the specification, and identifying corresponding elements in the allegedly anticipating reference. Idacon, Inc. v. Central Forest Products, Inc., 3 USPQ 2d 1079 (Dist. Ct., E.D. Oklahoma 1986).

Strandberg does not teach all the elements of the claimed invention. Claim 1, and all the rejected claims that depend upon claim 1, include the element of "and at least one other basic amino acid residue...substituted by a non-basic amino acid residue...". Thus the invention requires that a basic residue is substituted with a non-basic residue for the "other" residue besides "R275".

In Strandberg, the examples argued by the Action are the Arg-275-Glu,Asp-477-Glu and Arg-275-Glu,Asp-477-Asn variants. (Note the Action mistates that "glutamine", aka Gln, is substituted, when in fact it is recited as "t-PA/R15E,D194N", where "N" is asparagine (aka Asn), not Gln in the second

variant; see the abstract, or first paragraph of "Discussion") In each case, the "other" amino acid is "Asp", i.e., aspartic acid, a non-basic amino acid, being substituted.

Strandberg does not teach the substitution of a basic amino acid with a non-basic amino acid at the "other" residue, and therefore does not anticipate the claims.

V. Rejection Under 35 U.S.C. 103

Claims 1-17, 21, 25, 26, 28 and 30-32 were rejected under 35 U.S.C. § 103 as being unpatentable over Strandberg et al, in further view of Tate et al, Petersen et al, Lamba et al, Bennett et al, Anderson et al and Hassouna et al. These rejections are respectfully traversed.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 28 USPQ2d 1955 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings of the prior art itself would appear to have suggested the claimed subject matter to one of ordinary skill in the art. See In re Bell, 26 USPQ2d 1529 (Fed. Cir. 1993). If the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. See In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988). Thus, where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed

composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991). Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

To support a conclusion that a claimed combination is obvious, "either the references must expressly or impliedly suggest the claimed combination or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Int. 1985); see also Ex parte Kranz, 19 USPQ2d 1216, 1218 (Bd. Pat. App. & Int. 1991). Applicant respectfully submits that these requirements have not been met for the reasons discussed below.

As noted hereinabove for the anticipation rejection, one element of the claims is the substitution of a basic amino acid with a non-basic amino acid, in at least two positions in the tPA amino acid residue sequence, the first substitution necessarily being at position R275.

In addition, the claims require that the "other" residue substitution be located "in the serine protease region", ie., within residues 264-527 of tPA (see page 2, lines 7-9 of the specification).

The claims further require that the substitutions within the tPA variant disrupt "the salt bridge interaction between aspartate 477 and lysine 429".

Strandberg does not teach the substitution of a basic amino acid residue with a non-basic residue in the "other" residue position. Instead, Strandberg teaches that a salt bridge interaction involving residue "Asp 194" (ie., residue 477 in tPA terminology) is only a supported "hypothesis" based on the data (see second paragraph of "Discussion" at page 23447). Whereas Strandberg does modify enzymatic activity of the tPA variant by substitution of tPA residue 477, this result is carried out by substitution of a non-basic residue and not by substitution of a basic residue. Furthermore, as to the single chain construct wherein the tPA variant has R15E (corresponding to R275 in claim 1), Strandberg states that "Asp-194 [(i.e, Asp-477 on tPA)] does not play an essential role in the process" of stimulation of tPA by fibrin. Therefore, Strandberg does not describe nor suggest, either expressly or impliedly, that a substitution at a basic residue in the serine protease region would disrupt the salt bridge interaction between tPA residues 477 and 429 in a single chain variant of tPA.

Tate describes only a single variant, namely R275E, and does not teach nor impliedly suggest the substitution of a basic amino acid residue with a non-basic residue in the "other" residue position.

Bennett describes a large number of variants, but does not

describe the use of a second "other" residue substitution located in the serine protease region (i.e., tPA residues 264-527). Instead, Bennett describes the substitution of amino acids in the regions of residues 94, 95, 103, 117, 236, 238, 240 (see column 4, lines 33-60). Furthermore, Bennett does not describe nor suggest the specific substitution of a basic residue with a non-basic residue in the serine protease region.

Anderson describes a large number of variants such as those "in or around position 305" (column 8, lines 53-54), or having "one or more alterations in small regions of the protease domain...having charged amino acid side chains..." (Column 9, lines 52-54), also specifically identified as a large number of specific residues (column 9, lines 59-64). In all of the many, many constructs described, nowhere is there a specific description or suggestion that a tPA variant have both a substitution at residue R275 and in the serine protease region, nor does Anderson describe or suggest that both substitutions must be a substitution of a basic residue to a non-basic residue, as required by the claims.

Hassouna describes general clotting disorder assay methods, and does not describe in any way the preparation of a tPA variant. Therefore, there is no teaching in Hassouna that contributes to a suggestion of the structural elements of a tPA variant according to claim 1 as discussed herein.

Peterson describes several tPA variants, including several single-chain tPA variants having R275L. However, only one of

the numerous described tPA variants, namely R275L,K277L, includes the requirements 1) that both substitutions be from a basic to non-basic residue, 2) that the first substitution is to residue R275, and 3) that the "other" substitution be in the serine protease region (i.e, tPA residues 264-527). All other variants fall outside these claim criteria. Notwithstanding this disclosure by Peterson, it is noted that the R275L,K277L tPA variant is also outside the scope of claim 1 because it fails to meet the claim element of "disrupting the salt bridge interaction between aspartate 477 and lysine 429".

In particular, Peterson states in the abstract: "The amidolytic activity of [R275L,K277L]... was comparable to that of authentic one-chain tPA..." (See also page 3454, first paragraph, and Figure 2) indicating that this variant did not disrupt the salt bridge as required by the claims, thereby altering the catalytic activity. In this case, Peterson teaches away from the invention by showing a basic to non-basic substitution that is not functional as in Applicant's tPA variants.

Thus, Peterson not only does not describe either expressly or impliedly that the dual substitution of both R275 and a "other" basic residue with a non-basic amino acid is desirable, but Peterson also does not teach that such a substitution in the serine protease region can disrupt the salt bridge interaction between tPA residues 429 and 477 when used in combination with the R275 substitution.

Instead, Peterson shows other tPA variants that do quench amidolytic activity, but which do not include the substitution at R275 (see, for example K416S or K416,H417T).

Moreover, the Action mis-characterizes the teachings of Peterson by arguing that Peterson teaches that the "salt bridge formation between Asp-477 and basic residues Lys-277, Lys-429, Lys-416 or His-417 helps to stabilize the one-chain form of tPA that is responsible for the higher activity of the tPA zymogen..." (See first full paragraph on page 8 of the Action). In fact, Peterson shows no data with tPA variants of residue 429, and further Peterson concluded that the tPA variant at 277 "did not change the specific amidolytic activity significantly (Figure 2)" (see page 3454, first paragraph). This indicates that Peterson is not by its own data contributing to the notion that either residues 429 or 277 participate in a salt bridge with residue 477.

Furthermore, the Peterson data with tPA variants K416S and K416S,H417T do not indicate a role for 417, but only for 416. Peterson never states that 417 participates in a salt bridge, and never shows data with a 417 variant alone; the data always includes the combination of both the H417T with the K416S substitution, or K416S alone. Finally, Peterson never states that the H417T substitution contributes to the change in activities observed in the dual construct K416S,H417T, and it is noted that there is no difference identified by the authors between the measured activities of the single substitution K416S compared to the activities of the dual substitutions K416S,H417T, suggesting that the H417T substitution has no effect. This indicates that Peterson is not by its own data contributing to the notion that residue 417 participates in a salt bridge with residue 477.

Thus, Peterson only teaches that "Lys-416 <u>may</u> contribute significantly to the stabilization of an active conformation

of one-chain tPA; however, its presence is probably not an absolute requirement for obtaining one-chain activity" (see page 3456, second paragraph).

Therefore it is submitted that Peterson does not teach that residues 277, 429 or 417 participate in a salt bridge with residue 477 in a single-chain tPA variant; that Peterson does not teach the use of a substitution at R275 combined with a substitution in the serine protease region; and that Peterson does not teach the use of a substitution of a basic residue with a non-basic residue at both the R275 and the "other" residue position.

Lamba describes the three dimensional crystal structure of two-chain tPA. Lamba does not describe the structure of single-chain tPA, such as tPA/R275E, and does not expressly state that the salt bridges observed in the two-chain tPA structure would also occur in a single-chain tPA variant. Furthermore, although Lamba discusses a number of tPA variants (see page 126, second column to page 127, first paragraph), none of these involve R275, as required by the claims. Therefore, Lamba does not describe nor suggest that substitutions of a basic residue for a non-basic residue in the serine protease region of a tPA variant having a similar substitution at residue R275 would disrupt the salt bridge between residues 477 and 429 of a single-chain tPA variant.

The Action has argued as if the teachings of Lamba conclusively demonstrate that a salt bridge between tPA residues 429 and 477 "contributes to the unusually high catalytic activity of the one-chain form of tPA". However, Applicants respectfully disagree with this assertion since

Lamba does not make this conclusion, and the Action's statement is out of context and mis-states Lamba conclusions. In fact, Lamba did not describe the crystal structure of a single-chain tPA, but rather speculates that the salt bridge at residues 429 and 477 observed in the two-chain tPA crystal structure is "suggestive" and "may contribute to the unusually high catalytic activity of single chain tPA".

One skilled in the art cannot conclude that there is a reasonable expectation of success in practicing the claimed invention where the cited reference offers a "suggestion" of a structure that "may contribute" to activity, particularly where that structure is based on data from the crystal of a two-chain tPA, and Applicants are claiming a tPA variant that exists in a single-chain conformation by virtue of the claim element of a substitution at tPA position R275.

At best, the Lamba reference provides a suggestion to try to establish the presence of a salt bridge between tPA residues 429 and 477 of the single-chain tPA variant. Thus, the assertion that it would be obvious to use the cited disclosures to arrive at applicant's invention is nothing more than an "obvious to try" standard. This standard has continuously been determined by the courts to be an improper basis for rejection under 35 USC §103. In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988).

In its summary at pages 9-11, the Action argues the combined teachings of the references to arrive at its' conclusion of obviousness of the claimed invention. However, the analysis does not explicitly identify the claim elements listed and addressed hereinabove, nor does the analysis

identify the suggestion in the references to combine the teachings of the several elements to arrive at the claimed invention. Therefore, it is submitted that the Action has not met its burden to establish a prima facie case for obviousness, and it is requested that the rejections be withdrawn.

Specifically, the opening sentences at the top of the last paragraph on page 9 is a conclusion without support, and will be disregarded. No single reference teaches these recited elements, and thess first sentences do not explain the motivation to combine the elements of the claims from the different references. The "alterations" alluded to in the many references do many things to the tPA variants, but none identify the collected elements of the claimed invention, nor provide an expressly stated motivation to combine. The random suggestion to substitute with non-basic amino acids does not of itself indicate a specific motivation to use the two substitutions, both basic to non-basic, and in the specified locations of R275 and the "other" residue in the serine protease region according to the claims.

Regarding the analysis at page 10, the Action combines random facts and alleges to assemble a motivation to combine without identifying the source of the motivation. However, it is the teachings of the art that must suggest the combination of the elements to arrive at the claimed invention. The Action fails to identify the statements in the art which suggest such a combination.

For example, even though the R275 variant is known to form a stable one-chain tPA variant, there is no indication in the cited references that a basic to non-basic substitution in

the serine protease region in combination with the R275 substitution would produce the superior product of the claimed invention.

As discussed above, none of the Strandberg, Bennet or Houssana references describe or suggest the substitution of a basic residue with a non-basic residue. And further, none of the Anderson, Peterson, Tate or Lamba references describe or suggest the combined elements of 1) a R275 substitution, 2) a substitution at an "other" residue in the serine protease region, and 3)the requirement that both substitutions are basic to non-basic residues.

The general assertions that there are numerous possible salt bridges, that there are many target residues, both within the serine protease region (e.g., Anderson) and outside that region (e.g., Bennett), and that many, many variants have been constructed, are not sufficient to establish that one skilled in the art could arrive at the claimed invention with a reasonable expectation of success because none of the many iterations identify the combination of elements, nor suggest those combinations.

By the Action's own admission (" It would have been obvious...to optimize the substitutions...", [at page 10]), the specific combination of elements was not known nor suggested, but rather would have to be systematically tested to arrive at the present invention. However, there is no indication in the references or the Action's logic to indicate which optimizations should be tested. In fact, the references describe a huge number of variants, none of which involved the claimed combination of elements. It is submitted that there is no indication on the record why one

skilled in the art would be motivated to arrive at the claimed combination.

At best there is an invitation to try the many candidate combinations, but there is no indication in any of the references that the claimed combination would be successful. See, in particular, the example in Peterson where the tPA variant R275L,K277L did not produce a claimed variant, because it did not have the claimed activity, and therefore Peterson teaches away from the claimed invention and any reasonable expectation of success.

For the above reasons, it is submitted that the rejections of the claims for obviousness in view of the cited references should be withdrawn.

The application in now believed to be in proper condition for allowance and an early notification of allowance is earnestly solicited. The Examiner is invited to telephone the undersigned if discussions are deemed to be helpful to advance the application.

Respectfully Submitted,

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